SCHEDULE 2

Degree of Fluctuation =
$$\frac{C^{ss}_{max} - C^{ss}_{min}}{C^{ss}_{min}} * 100 \%$$

Where

$$C^{ss}_{\text{max}} = \frac{FDose}{V_d} \left(\frac{1}{1 - e^{-k\tau}} \right) e^{-kt'_p} , \text{ with } t'_p = 2.303 * \log \frac{k_a (1 - e^{-k\tau}) / k (1 - e^{-k_a \tau})}{k_a - k}$$

$$C^{ss}_{min} = \frac{k_a F Dose}{V_d(k_a - k)} \left(\frac{1}{1 - e^{-k\tau}}\right) e^{-k\tau}$$

F = Fraction Absorbed

 k_a = Absorption Rate Constant

k = Elimination Rate Constant

 V_d = Apparent Volume of Distribution

 τ = Dosing Interval

By substituting the above C_{max}^{ss} and C_{min}^{ss} equations into the Degree of Fluctuation equation:

Degree of Fluctuation
$$= \frac{\left(\frac{FDose}{V_d}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt'_p}\right) - \left(\frac{k_aFDose}{V_d(k_a-k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}\right)}{\frac{k_aFDose}{V_d(k_a-k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}} * 100\%$$

$$\Rightarrow \frac{FDose}{V_d} \left[\left(\frac{1}{1 - e^{-k\tau}} \right) e^{-kt'_p} - \left(\frac{k_a}{(k_a - k)} \left(\frac{1}{1 - e^{-k\tau}} \right) e^{-k\tau} \right) \right] * 100\%$$

$$\frac{FDose}{V_d} \left(\frac{k_a}{(k_a - k)} \left(\frac{1}{1 - e^{-k\tau}} \right) e^{-k\tau} \right)$$

By canceling out the term
$$\frac{FDose}{V_d}$$
 \Rightarrow $\frac{\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau'_p} - \left(\frac{k_a}{(k_a-k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}\right)}{\frac{k_a}{(k_a-k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}}$ * 100 %

Rearranging the equation further
$$\Rightarrow \frac{\frac{1}{1-e^{-kr}}\left(e^{-kr'_p} - \frac{k_a}{(k_a - k)}e^{-kr}\right)}{\frac{1}{1-e^{-kr}}\left(\frac{k_a}{(k_a - k)}e^{-kr}\right)} * 100 \%$$

Finally, by cancelling out the term
$$\frac{1}{1 - e^{-k\tau}} \rightarrow \frac{\left(e^{-kt'_p} - \frac{k_a}{(k_a - k)}e^{-k\tau}\right)}{\left(\frac{k_a}{(k_a - k)}e^{-k\tau}\right)} * 100 \%$$

$$\therefore \text{ Degree of Fluctuation} = \frac{\left(e^{-kt'_p} - \frac{k_a}{(k_a - k)}e^{-k\tau}\right)}{\left(\frac{k_a}{(k_a - k)}e^{-k\tau}\right)} * 100 \%$$

CONCLUSION:

- Degree of Fluctuation is dose independent
- Degree of Fluctuation is dependent on absorption and elimination rates and the dosing interval